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1. Your reference	GWS\21249
2. Patent application number *(The Patent Office will fill in this part)*	**9903394.6** 15 FEB 1999
3. Full name, address and postcode of the or of each applicant *(underline all surnames)*	Avimo Group Limited 34 Bukit Pasoh Road Singapore 08948
Patents ADP number *(if you know it)*	7194053001
If the applicant is a corporate body, give the country/state of its incorporation	Republic of Singapore
4. Title of the invention	Treatment of neovascularization and other eye diseases
5. Name of your agent *(if you have one)* "Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*	MATHYS & SQUIRE 100 Grays Inn Road London WC1X 8AL
Patents ADP number *(if you know it)*	1081001

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Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

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Continuation sheets of this form	
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Claim(s)	3
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Priority documents	-
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Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	-
Request for preliminary examination and search *(Patents Form 9/77)*	-
Request for substantive examination *(Patents Form 10/77)*	-
Any other documents *(please specify)*	-

11. I/We request the grant of a patent on the basis of this application.

Signature: Mathys & Squire

Date: 15 February 1999

12. Name and daytime telephone number of person to contact in the United Kingdom

George W Schlich 0171 830 0000

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TREATMENT OF NEOVASCULARIZATION AND OTHER EYE DISEASES

The present invention relates to methods and apparatus for treatment of neovascularization and other eye diseases.

Age-related Macular Degeneration (AMD) is a chronic disease affecting primarily the choriocapillaris, Bruch's membrane and the Retinal Pigment Epithelium (RPE). It is the most common cause of legal blindness in patients aged 65 and over in the US, Canada, England, Wales, Scotland and Australia. Although the average age of patients when they lose central vision in the first eye is 65 years, some patients develop evidence of the disease in their fourth or fifth decade of life.

Approximately 10% to 15% of the patients manifest the exudative form of the disease. Exudative AMD accounted for 79% of legally blind eyes. The disease is bilateral with accumulating chances of approximately 10% to 15% per annum of developing the blinding disorder in the fellow eye. The recurrence rate of a treated membrane is estimated to be 50% within 18 months.

The hallmark of the exudative form of the disease is a Choroidal Neo-Vascular Membrane (CNVM) that grows beneath the retina or the RPE in the foveal-macular region. This CNVM leaks and bleeds and evokes a scaring reaction that eventually results in the scaring of the affected area with consequential blindness. Histopathology of these CNVMs revealed that the vast majority of the membranes had few (1 to 3) feeder vessels only. It means that only a few "vascular bridges" connect the origin of the CNVM (in the choroid) to the new location beneath the retina or the RPE.

The currently available treatment, as recommended by the Macular Photocoagulation Study (MPS) is massive destruction of the membrane with an appropriate laser. Unfortunately, most of the membranes are

sub-foveal when discovered and such a treatment modality leads to the complete destruction of all tissues - CNVM and retinal - within the treated area. It has been suggested that focusing on feeder vessel destruction will minimize the collateral damage caused by the massive tissue ablation. The major problem with this treatment is the limited patient eligibility because of the difficulty in identifying feeder vessels.

Thus existing techniques for treatment of AMD can not treat the disease satisfactorily, the known techniques routinely damage blood vessels and tissue unrelated to disease or disease-causing areas. Essentially, the techniques lack the ability to locate and destroy feeder vessels to the neovascularization with sufficient accuracy.

It is an object of the present invention to provide methods and apparatus for treatment of neovascularization that overcome or at least ameliorate the disadvantages identified.

Accordingly, a first aspect of the invention provides a method of treating neovascularization in an eye of a patient, comprising:-

(i) introducing a detectable marker into the circulation of the patient at a point remote from the eye;

(ii) observing a region of suspect neovascularization in the eye after introduction of the marker so as to detect the first appearance of the marker in that region;

(iii) determining from the location or locations of first appearance of the marker the location or locations of one or more blood vessels feeding blood into the region; and

(iv) treating the blood vessel to prevent it feeding blood into the region.

Apparatus suitable for implementing the method is described in WO-A-98/46122, the contents of which are incorporated herein by reference.

Typically, the detectable marker is a fluorescent dye, the region is illuminated by radiation that excites the dye and the first appearance of the dye in the region is detected as an increase in brightness by a predetermined amount above background levels. In an example of the invention in use, a video image of the region is monitored for appearance of the dye. Initially, the image is dark, indicating that no fluorescent dye has entered a blood vessel contributing to the image. As soon as dye enters the field of the image, it is visible as an area of increased brightness and its position is readily seen and recorded.

As the time between first appearance of the marker with just one or a small number of areas of brightness on the image and the filling of most of the image with dye is usually very short, of the order of fractions of a second, it is preferred that the region is observed by recording a succession of images of the region using an image recorder and subsequently examining the recorded images to identify the location of a blood vessel feeding blood into the region. This enables a user to store images for later examination. A suitable rate of capture of images is at least 30, though it is preferred that the rate is at least 45 per second, and higher rates such as 60 per second and greater will tend to give improved identification of feeder blood vessel location.

In an embodiment of the invention, recording of images of the region is triggered by trigger means associated with the image recorder and sensitive to an increase of the marker in the region. The trigger can be set so as to trigger image capture when the brightness level rises above the average background level plus a predetermined amount. This may be initially set at a level of, say, 10 per cent but is usually optimized empirically. Computer memory usage for image storage is relatively high, and thus this embodiment is of benefit in that unnecessary storage of images prior to first appearance of dye in the region is reduced and may even be avoided.

In a further embodiment of the invention, the method additionally comprises introducing a second detectable marker into the circulation of the patient, and detecting the location of the second detectable marker in the region so as to determine position of blood vessel walls in the region. This second marker is generally used to identify blood vessels throughout the region, so as to build up a map or network of the vasculature especially the blood vessel walls of the feeder vessels suspected of causing or contributing to disease. This second detectable marker can be used in real time, not needing the fast image capture of the first marker. In use, the image or images showing the location of the first appearance of the first detectable marker into the region are compared with the position of the blood vessel walls located by the second detectable marker, such as by overlaying one onto the other, so that it is possible to determine the location of a blood vessel feeding blood into the region. This introduces further accuracy into identification of the feeders, for example if the CNVM is under examination the stained blood vessel walls can be compared with the positions of the first fillings of the region and only those overlapping areas be considered as feeder vessels to be treated.

Treatment may be by conventional laser and is generally aimed at destroying the feeder blood vessel identified. In addition, it is a preferred embodiment of the invention that the treatment is carried out using a laser having the same absorption wave band of the second detectable marker.

In a second aspect of the invention there is provided apparatus for examination of neovascularization in an eye of a patient, comprising:-

a light source for exciting a dye introduced into the circulation of the patient;

an image generator for generating an image of a region of the eye under examination; and

an image recorder for recording a plurality of images of the region.

The image recorder preferably records images at a rate of at least 30 per second, or faster.

In a particularly preferred embodiment of the invention, the apparatus further comprises a trigger means associated with the image recorder and sensitive to an increase in marker in the region, wherein it triggers image recording in response to an increase in marker in the region above a predetermined level.

Thus using the method of the invention, in order to locate a target, it is not necessary to see the target, as long as the target is marked or contrasted or is easily differentiated from the background by a visible marker, e.g. a dye.

The distribution of the marker inside the target region, such as the CNVM, always starts at the feeder or feeders. Consequently, the more closely temporally-spaced images are captured during the first second of the marker's entry into the CNVM, the better the chances of locating and confirming the feeders' origin(s). The invention may use very high speed image capture now technologically available to obtain improved identification of the feeder vessels.

It has been found that magnification is more important than resolution when searching for a feeder vessel. In preferred embodiments of the invention, an operator may trade off a decision not to pursue higher resolution to enable a better view of a feeder. Preferably, accurate destruction of the feeders should be performed immediately once they are identified, and the invention advantageously provides for these functions both to be incorporated in one instrument.

In a specific embodiment of the invention, two fluorescent dyes, ICG and fluorescein, are injected into the circulation (simultaneously or separately)

as is done in any current angiographic imaging procedure. At the earliest entrance of the fluorescein into the choroidal circulation, the increase in the brightness of the background haze is detected by the instrument which then automatically self-triggers the image acquisition. The very earliest filling of the CNVM is acquired as fast as possible using a (digital) camera operating at a rate of 60 frames per second. The faster the image acquisition, the better the details of the earliest appearance of the dye, the better the ability to locate and confirm the feeder vessels. All the images acquired during this early phase are presented on the computer monitor to be studied by the instrument operator(s). The earliest images that show the entry of the fluorescein into the CNVM are isolated and stored as individual frames (marked or numbered or both) in the computer memory.

Image processing (software) is then used to analyze and enhance the location(s) where the fluorescein starts its entry into the CNVM. While executing this procedure of analysing fluorescein early filling, the second marker, ICG, is staining the vessel walls of the CNVM. This staining process is being monitored, in real time, by the instrument operator(s). The stored image(s) of the first, fluorescein, marker's early filling is recalled, made semi-transparent and then overlaid or otherwise superimposed on the real-time image of the ongoing staining of the membrane by the second marker. Only the stained vessels of the CNVM that are within the marked areas of the stored early filling images are to be considered as possible feeders. A $\phi 100 \mu m$ laser spot of appropriate power is aimed directly at the suspected feeder(s) and the treatment mode is executed. An aiming beam enables accurate laser shots to be applied to the target(s).

The wavebands of the laser used for the treatment and the aiming is the same as that needed to excite/activate the fluorescent marker (ICG) that stains the vessel walls of the CNVM. In this way, it is possible to combine better targeting and better treatment with lower powers due to enhancement in absorption (of laser energy) by the second marker.

The instrument itself may also include a self-tracking system that uses the large vessels at the rim of the optic disc as alignment reference points in order to overcome the patient's unintentional eye movements.

The method of the invention is found to produce good results as it enables high magnification of the CNVM (while compromising on resolution). This "trade-off" is possible in embodiments of the invention because the targets are marked with fluorescent markers.

The overlaying of the locations of early filling obtained by the first marker on the real-time image showing the staining of the CNVM walls by the second marker enables identification and confirmation of the feeder vessels that contribute to disease. These specific vessels may then be considered for laser treatment without massive destruction of areas of healthy vasculature and tissue.

The use of a laser that emits at the same waveband as the excitation waveband of the marker that stains the vessel walls confers the further benefit of less collateral damage due to the lower laser power needed to block the stained vessels.

The "self-tracking" of embodiments of the invention is like computerized finger-print recognition, at the first level. It may be achieved using the following steps. The computer remembers a "map" (image) with key (user-registered) landmarks. Upon receiving a new image (live or still), it uses that (stored) map, rotates it, scales it, or uses any (known) means to find out if the new image is the same as the map. The "self-tracking" has 2 parts: (1) once the first (map) image is registered (in memory) with its landmarks (eg where major vessels emanate from the edge of the optic disc), the software must find the same location every time (and maybe, be able to move the machine to the re-oriented map position), and (2) if required to zoom in on a specific area within the new image, the software

must triangulate (based on the map landmarks) and memorize the coordinates so as to zoom in, (and maybe later, zoom out to the previous image). It must also keep the machine pointed at the same spot during any operations.

There now follows description of specific embodiments of the invention to illustrate the invention in a non-limiting way.

EXAMPLE 1

A flow chart of a method of the invention is thus:-

Main Start
↓
Fluorescein Sequence
↓
ICG Sequence
↓
Treatment Sequence
↓
PDT Sequence

In more detail, a method of the invention is carried out as follows.

MAIN START

The patient is prepared :

Measure the curvature of the cornea for the best-fitting (or closest-fitting) contact lens to use.

Dilate pupil, insert lid retractor and complete lens fitting.

Adjust fixation light, head-chin rest and seat height to pose patient in appropriate position and as comfortably as possible.

Insert intravenous tap (through which dye can be injected) usually at the back of hand.

FLUORESCEIN SEQUENCE

Use "general illumination" (any colour) to aim at the appropriate area, adjusting illumination intensity, magnification and focus (in any order) to achieve the required field of view and details. (Illumination is adjusted to appropriate minimum levels such that clear, low-noise images can be seen, ie no exact magnitude as it depends on the optics and media of the machine and the human eye. The images are black and white, using grey level determination.)

Usually, use low magnification (and therefore wider field) to begin.

Once the general (or specific area) is in focus, change filters to appropriate set (blue excitation, $\lambda = 480$-495nm; green barrier, $\lambda = 515$-535nm) for fluorescein.

Prepare triggering software :
Preset to capture images at maximum frame rate (60 full frames per second minimum because of blood flow rate – it takes 10-25s after injection for dye to arrive in eye) for maximum length of time (3s minimum, ie total 180 frames minimum – longer if possible). (See EXAMPLE 2 below.)

Take a background scan of the image using the chosen filter set. The image is black (if no fluorescein is present) as the barrier filter does not pass the blue excitation illumination.

Set triggering threshold to be background level plus xx units, wherein xx is empirically established or estimated. The units are usually grey levels. The threshold is usually the average brightness of the entire image or the diagonal strips of pixels across the image – depending on such factors as

the speed of the computer or the time CPU allowed for averaging operations. Or, any other sensitive measure of brightness changes in an image.) Hence, the threshold is relative to the "background" (brightness) plus xx. It does not matter if the dye is already present; only the increase in the signal (above the first recorded "background") is needed for threshold-trigger. (See Comments below for an alternative to this threshold-triggering.)

Inject 3-4ml of fluorescein through intravenous tap.

On appearance of fluorescein in the field of view (FoV – focal plane), and at an image brightness equal to or higher than the threshold, the evolving filling of the vessels in the FoV is captured and stored in the computer memory. Only a few (consecutive) frames (<10), when the fluorescein signal begins to appear and increase (in the vessels) are useful. It suggests the location(s) of the feeder vessels (as they are filled first). The rest of the frame should remain darker (as they are yet to be filled at this time). The fluorescein filling begins in the choroid (below the retina). However, the Retinal Pigment Epithelium (RPE – the pigmented layer between the choroid and the retina) blocks (or strongly and significantly attenuates) the excitation illumination from reaching the choroid. The RPE also blocks the fluorescein fluorescence (if any) from the choroid. The feeders protrude past the RPE to feed the associated membranes in the sub-retina. These feeders followed by the membranes will fill after the choroid but before the retinal vessels flash. The time lapse between choroidal and retinal filling is (usually) less than 100 milliseconds. Hence, expect to see black, then sudden bright flash (as retina vessels fill). (Blink response is estimated to be about 250ms.) If triggering sequence is correctly captured, expect to see either (1) spots or lines indicating where the feeders fill; followed by a spreading (fanning) out of the filling into patches in the immediate neighbourhood of the spots or lines (feeder vessels), or, (2) spots and lines fill, followed by a spreading out of the filling, centred about the spots and

lines, until the spots and lines disappear in the brightening patches. Thus, in the few consecutive frames will be captured the location of the first filling of the spots and lines which will be the suspect feeders. After that, the capillaries-membranes fill – overwhelming the feeder locations or not – then the retinal vasculature begins to fill and the entire image details are overwhelmed by a bright flash.

The captured sequence (180 frames) are displayed for the operator to view, to locate suspected feeder(s) – the spots and lines.

The few (<10) frames are (image-processed to increase image clarity, if needed, and) stored in permanent memory (hard disk). The entire captured sequence can also be saved, as desired. Eg for demonstration purposes.

Repeat the injection and image-capture sequence, if imaging is unsatisfactory. Use another 2-3ml of fluorescein. Note that the already present fluorescein will contribute to the higher background "noise".

ICG SEQUENCE

Revert to "general illumination" and adjust intensity, focus and magnification on suspect area(s) – those determined by the fluorescein early filling.

Change filter set for ICG; change illumination to infra-red (IR: $\lambda = 780$-790nm); barrier ($\lambda = 810$-880nm).

Adjust IR illumination intensity – usually low; depends on optics, media and amount to ICG to be injected.

ICG early filling is unlike the patchy fluorescein filling. Captured images have higher contrast, showing the sequential filling from choroidal to the inflow (arterial), fine filling of the capillaries-membranes and outflow

(venous) of the feeders, then retinal vasculature. This allows for 2-dimensional-3-dimensional reconstruction of the sequentially captured images to visualize the structure – direction of vessel growth, for example – of the feeders and the capillaries-membranes.

Variation A

Prepare software (as before for fluorescein).

Capture ICG early filling sequence for comparison to fluorescein to confirm location(s) of feeders.

Inject 2-3ml of ICG (through the intravenous tap).

Capture early filling (as before for fluorescein). The image is black before ICG arrival. When ICG arrives, will see choroidal flash, followed by the filling feeders, spreading out from arterial to venous, then retinal.

Store captured sequence or frames as required (as in Fluorescein Sequence).

Variation B

Select stored, early-fluorescein-filling frame(s).

Overlay on the "live" image (at the same magnification, orientation). (See "self-tracking")

Inject 2-3ml of ICG (through the intravenous tap).

Observe ICG filling and staining of vessels under the superimposed (fluorescein frame).

Variation C

Inject 2-3ml of ICG (through the intravenous tap).

Observe and capture (no need to trigger-capture) the inflow and outflow of ICG through the (particular area of the) circulation – filling from arterial to venous sides of the feeder and membranes. Can see where and how ICG bolus moves through the circulation – thereby locating the feeder (arterial) input into the membrane.

ICG fills vessels, then is removed from circulation. However, ICG stains diseased vessels (feeders) so that as time elapses, only the ICG-stained feeders will remain visible – adjust illumination intensity accordingly; the non-pathological circulation will fade out of view (in about 3-5 minutes post-injection).

Feeder locations are thus confirmed.

Maintain the same filter set, adjusting IR illumination as needed.

TREATMENT SEQUENCE

Move treatment laser aiming beam ($\lambda = 633$nm) to the location of feeder(s) – ICG-stained spots (usually arterial first, if can be determined).

Adjust treatment laser power and pulse duration. (Magnitudes are empirically established or estimated.) Usually, start at lower power-duration, then increase until required effect is seen on live image. (Usually no more than 1000mW for up to 300ms per pulse is used.) Alternatively, fix power-duration but repeat pulsing until required effect is seen. (No fixed number of pulses.)

Can flush with small amount (1-2ml) of ICG (to increase signal).

Fire treatment laser on targeted feeder (until effect is seen, if possible). The treatment ($\lambda = 810$nm) laser delivers thermal (IR) energy to the target. It literally burns the feeders. Hence, it becomes important that the treatment spot be very concentrated ($<\phi 100\mu$m) to deliver a high concentration of thermal energy and to ensure that collateral damage – damage to the neighbouring areas about and beyond the laser spot – is minimized, ie only the feeder is burned.

Inject small amount (1-2ml) of ICG to look for immediate confirmation of laser effect. If treatment is effective, feeder is blocked and membrane does not fill (with ICG).

Depending on the FoV, the sequence may be repeated at other areas. (See "self-tracking".)

PHOTO-DYNAMIC THERAPY

A Photo-Dynamic Therapy (PDT) – type sequence can be inserted at the end of the Treatment Sequence.

PDT uses a photo-sensitizer to enhance the absorption of specific wavelengths (wavebands) of illumination. Such a photo-sensitizer is ideally absorbed or adsorbed (stains) in the areas to be treated (thermally burned, in this case). The photo-sensitizer does not stain healthy areas. The stained pathological areas are exposed to the sensitizer's waveband at low powers for long durations. ICG can be such a photo-sensitizer in our application. The low power can be at the illumination levels or slightly more (but <50mW, for example). The value is not exactly known (depending on staining, optics and media).

The excitation IR illumination is close to or can be the same as the treatment laser wavelength (or waveband). (This is because the overlap of ICG excitation and ICG fluorescence wavebands is relatively large. Each

waveband, by itself, spans more than 100nm.) The difference between illumination and treatment beams is that the continuous illumination is at much lower power and/or is much more diffused; while the treatment beam is much more focused ($< \phi 100 \mu m$ treatment beam spot) and at much higher pulsed powers (up to 2000mW.)

ICG stains the capillaries in the membrane as well as the larger feeder-vessels. At low IR power, the feeders themselves cannot be burned (must use the ICG and Treatment Sequences for the larger feeders). However, it may be possible to destroy the membrane capillaries using this long, low-power exposure. As such, the entire ICG and Treatment Sequences, in fact, partly serve as the PDT Sequence as well (even if the PDT Sequence described below is not used). This is because the continuous, diffused, low-power, ICG-excitation, IR illumination is always present in these 2 sequences. Hence, depending on the duration of the ICG and Treatment Sequences, the capillaries-membranes are in effect being treated as well. (The ICG and Treatment Sequences are meant to locate and destroy the feeders only. Note that the feeder signals may be harder to extract in the presence of nearby or overlaying membranes.)

If indeed possible, the patient may leave after this low-power exposure, ie the sequence may be interrupted. After 1 to 2 weeks, the patient should be recalled for all the above sequences. If the PDT Sequence is successful, the capillaries, and therefore the membrane, do not accept (fluorescein and) ICG : they do not fill and no signal is emitted. However, the larger undamaged feeders will remain and will be stained and be fluorescent. The advantage of this is that the background noise is reduced (as the once-surrounding membrane does not fluoresce). The feeders are more easily and more exactly located and more distinctly seen so that the Treatment Sequence can be better applied.

In this manner, the capillaries-membranes are first destroyed as part of the

procedure of locating the feeders. Then, the feeders are targeted and destroyed in the follow-up.

PDT SEQUENCE

Revert to "general illumination" and adjust intensity, focus and magnification on suspect area(s) – those determined by the fluorescein early filling, or, broad areas without specific targets.

Change (or maintain) filter set for ICG and infra-red illumination (IR:$\lambda = 780$-790nm).

Adjust IR illumination intensity slightly higher than before (but <50mW) – depends on optics, media and amount to ICG to be injected.

Inject (up to 10ml) of ICG, if needed, (determined by factors such as patient's body weight).

Expose to IR for extended periods (>15 minutes). Exposure duration not known but must be at low power.

Variation A

The PDT Sequence can be carried out after executing the ICG and Treatment Sequences because the diseased capillaries-membrane are not treated – too small or too fine, over too wide areas for the Treatment Sequence to be applied. Hence, apply PDT Sequence after feeder treatment to destroy the remaining capillaries-membranes.

Variation B

The PDT Sequence can be carried out before executing the Treatment Sequence, especially if feeders cannot be clearly located because they are hidden by the overlaying capillaries-membranes. In this case, apply PDT Sequence to destroy the capillaries-membranes to reduce their "noise"

contribution to the image so that the underlying feeders can be more clearly defined by a re-execution of the Fluorescein and ICG Sequences (maybe 1 or 2 weeks after the PDT Sequence).

EXAMPLE 2

Example 1 is repeated using very large (image) storage memory as an alternative to threshold triggering. Upon injection of any dye, the system immediately begins to capture and store all incoming images (at 60 frames per second or faster). With ample memory which provides the needed extended period of image capturing, the early filling is captured within 10-15s from injection. This takes care of false triggering due to over-sensitive threshold, or, no (or late) triggering due to overly high threshold setting (ie xx set too large).

The invention thus provides methods for identifying and treating neovascularization such as in AMD.

Claims

1. A method of treating neovascularization in an eye of a patient, comprising:-

(i) introducing a detectable marker into the circulation of the patient at a point remote from the eye;

(ii) observing a region of neovascularization in the eye after introduction of the marker so as to detect the first appearance of the marker in that region;

(iii) determining from the location of first appearance of the marker the location of a blood vessel feeding blood into the region; and

(iv) treating the blood vessel to prevent it feeding blood into the region.

2. A method according to Claim 1, wherein the detectable marker is a fluorescent dye, the region is illuminated by radiation that excites the dye and the first appearance of the dye in the region is detected as an increase in brightness by a predetermined amount above background levels.

3. A method according to Claim 1 or 2, for treating neovascularization in a Choroidal Neo-Vascular Membrane (CNVM).

4. A method according to any of Claims 1 to 3, wherein the region is observed by recording a succession of images of the region using an image recorder and subsequently examining the recorded images to identify the location of a blood vessel feeding blood into the region.

5. A method according to Claim 4, wherein the image recorder captures images at a rate of at least 30 per second.

6. A method according to Claim 4 or 5, wherein recording of images of the region is triggered by trigger means associated with the image recorder

and sensitive to an increase of the marker in the region.

7. A method according to any of Claims 1 to 6, wherein the blood vessel is treated by blocking it using a laser.

8. A method according to any of Claims 1 to 7, further comprising introducing a second detectable marker into the circulation of the patient, and detecting the location of the second detectable marker in the region so as to determine position of blood vessel walls in the region.

9. A method according to Claim 8, comprising comparing the location of the first appearance of the first detectable marker into the region with the position of the blood vessel walls located by the second detectable marker to determine and/or confirm the location of a blood vessel feeding blood into the region.

10. A method according to any of Claims 7 to 9, comprising treating the blood vessel using a laser wherein the waveband of the laser is the same as the wave band of the second detectable marker.

11. A method according to any of Claims 1 to 10, comprising treating the blood vessels by photo-dynamic therapy.

12. Apparatus for examination of neovascularization in an eye of a patient, comprising:-

a light source for exciting a dye introduced into the circulation of the patient;

an image generator for generating an image of a region of the eye under examination; and

an image recorder for recording a plurality of images of the region.

13. Apparatus according to Claim 12, wherein the image recorder can

record images at a rate of at least 30 per second.

14. Apparatus according to Claim 12 or 13, further comprising a trigger means associated with the image recorder and sensitive to an increase in marker in the region, wherein it triggers image recording in response to an increase in marker in the region above a predetermined level.

15. A method of treating neovascularization in an eye of a patient substantially as hereinbefore described.